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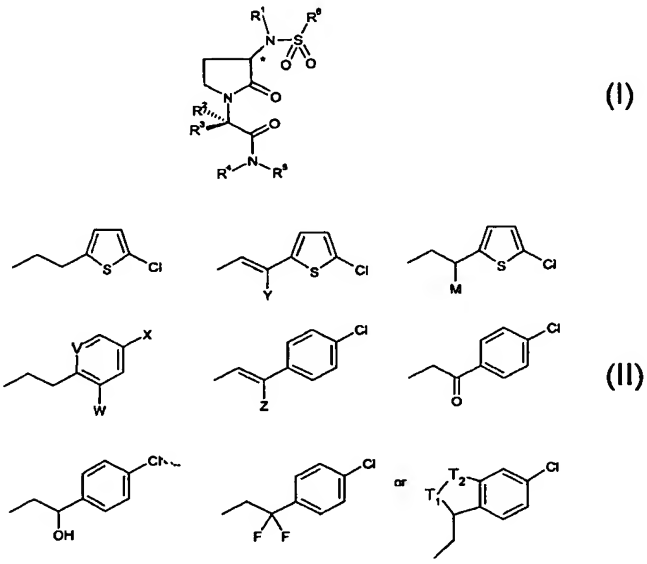
(54) Title: PYRROLYDIN-2-ONE DERIVATIVES AS INHIBITORS OF THROMBIN AND FACTOR XA



(I)

(II)

(57) Abstract: The invention relates to compounds of formula (I), wherein : R^1 represents hydrogen, C_{1-4} alkyl, $-CH_2CO_2H$, $-CH_2CO_2C_{1-2}$alkyl, or $-CH_2CONR7R^8$; R^2 and R^3 independently represent hydrogen, $-C_{1-6}$alkyl, $-C_{1-3}$alkylCN, $-C_{1-3}$alkylCO_2H, $-C_{1-4}$alkylOC_{1-4}alkyl, $-C_{1-4}$alkyl$S(O)_nC_{1-4}$alkyl, $-C_{1-4}$alkyl$NR^{10}R^{11}$, $-C_{1-3}$alkylNCO_2C_{1-4}alkyl, $-C_{1-3}$alkyl$CONR^7R^8$, $-C_{1-3}$alkylCO_2C_{0-2}alkylR^9, $-C_{1-3}$alkylCOC_{0-2}alkylR^9, $-C_{1-3}$alkyl$CON(R^8)C_{0-2}$alkylR^9, $-C_{1-3}$alkylNCO_2C_{0-2}alkylR^9, $-C_{1-3}$alkyl$NCOC_{0-2}$alkylR^9 or $-C_{0-2}$alkylR^9, with the proviso that one of R^2 and R^3 is hydrogen and the other is a substituent other than hydrogen; n is an integer between 0 and 2; R^4 and R^5 together with the nitrogen atom to which they are attached form a morpholino ring; R^6 represents a group selected from formula (II) wherein T_1 and T_2 independently represent CH_2, NH, S or O with the proviso that when one of T_1 or T_2 represents NH, S or O the other represents CH_2; M represents CH_3, -OH or PO; V represents CH or N; W represents H, CH_3, Cl or F; X represents Cl, Br, F or $-CH_3$; Y represents CH_3 or CF_3; Z represents $-CH_3$ or F; R^7 and R^8 are independently hydrogen, C_{1-4}alkyl or together with the N atom to which they are bonded form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom selected from O, N or S; R^{10} and R^{11} independently represent C_{1-4}alkyl or together with the N atom towhich they are bonded form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additionalheteroatom selected from O, N or S; R^9 represents phenyl or a 5- or 6- membered aromatic or non-aromatic heterocyclic group, containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: C_{1-3}alkyl or halogen; and pharmaceutically acceptable derivatives thereof, processes for their preparation, pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a thrombin inhibitor is indicated.

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